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Emerging Role of PML Nuclear Bodies in Innate Immune Signaling

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Research in the last 2 decades has demonstrated that a specific organelle of the cell nucleus, termed PML nuclear body (PML-NB) or nuclear domain 10 (ND10), is frequently modified during viral infection. This correlates with antagonization of a direct repressive function of individual PML-NB components, such as the PML, hDaxx, Sp100, or ATRX protein, that are able to act as cellular restriction factors. Recent studies now reveal an emerging role of PML-NBs as coregulatory structures of both type I and type II interferon responses. This emphasizes that targeting of PML-NBs by viral regulatory proteins has evolved as a strategy to compromise intrinsic antiviral defense and innate immune responses.

Promyelocytic leukemia (PML) protein, a member of the tripartite motif (TRIM) protein family, is the key component of subnuclear structures known as PML nuclear bodies (PML-NBs) or nuclear domains 10 (ND10). PML-NBs are dynamic foci that consist of numerous permanently or transiently associated proteins and, consequently, have been implicated in the regulation of diverse cellular functions, including the cell cycle, apoptosis, senescence, stress, and DNA damage responses (reviewed in reference 1). Although the underlying biochemical function of these subnuclear structures is still unclear, three models can be found in the literature, proposing PML-NBs to be nuclear protein depots, sites of nuclear activities (e.g., transcription), or hotspots for posttranslational modifications. In particular, since nearly all PML-associated proteins are modified by SUMO and SUMOylation of PML is essential for the integrity of PML-NBs, these structures may form "catalytic surfaces" for SUMOylation (1). This is of importance since recent studies suggest that the SUMO pathway is required for the regulation of innate immune signaling and intrinsic immunity during viral infection (reviewed in reference 2). The observation that PML-NBs are targeted and modified by many viruses during infection set off a longstanding debate as to whether PML-NBs exert a pro- or antiviral function and led to a fruitful area of virology research over the past 20 years. Interestingly, these studies revealed that viruses, even representatives of the same virus family, trigger diverse modifications of PML-NBs during infection, ranging from proteasomal degradation of NB components by herpes simplex virus type 1 (HSV-1), to dispersal of PML-NBs by human cytomegalovirus (HCMV), to a rearrangement of PML-NB foci into nuclear track-like structures by adenoviruses or a relocalization of PML into cytoplasmic bodies by HIV-1 (3–5). While there are a few examples of viral factors that undergo interactions with PML-NBs in order to exploit these structures for the benefit of the virus, the main body of evidence supports a role of PML-NBs as components of the antiviral defense against a variety of DNA and RNA viruses (reviewed in reference 3).

PML-NBs AND INTRINSIC IMMUNITY

The role of PML-NBs in intrinsic immunity, which represents the first line of intracellular defense against invading pathogens, has been discovered and extensively characterized in the context of herpesviral infections (3, 6). As observed for many nuclear-replicating viruses, the genomes of herpesviruses like HSV-1 or HCMV become associated with PML-NBs as soon as they enter the nucleus. This association results in epigenetic silencing of viral genomes and, thus, affects one of the first steps of the herpesviral life cycle (Fig. 1). Employment of the small interfering RNA (siRNA) technology in numerous studies by our and other groups has convincingly demonstrated that several NB proteins, including PML, hDaxx, Sp100, and ATRX, act as cellular restriction factors and contribute to this repression process in a cooperative manner (6). A different restriction mechanism, acting on a later stage of viral infection, has been found to affect the herpesvirus varicella-zoster virus (VZV). During VZV infection, enlarged PML-NBs entrap newly assembled VZV nucleocapsids, based on the interaction of one specific PML isoform with the open reading frame 23 (ORF23) capsid protein, and prevent their nuclear egress (7). This indicates that PML-NBs can inhibit viral replication by mechanistically different modes of action ranging from chromatin modification to physical entrapment.

Evidence continues to accumulate that the restricting activity of NB proteins not only extends to further DNA viruses, including adeno-, papilloma- and parvoviruses, but also affects specific processes in the life cycle of cytoplasmically replicating RNA viruses (8–11). While *in vivo* experiments with PML knockout mice demonstrated restriction of the arenavirus lymphocytic choriomeningitis virus (LCMV) and the rhabdovirus vesicular stomatitis virus (VSV) more than a decade ago, convincing data for an involvement of PML in HIV-1 restriction were only recently provided by two publications (4, 5). They report that PML-NBs undergo a rapid relocalization into cytoplasmic bodies after infection with HIV-1 and other retroviruses, thus enabling an interference with early viral events in the cytoplasm. Both studies agree that PML restricts HIV-1 at the level of reverse transcription, but the underlying mechanism remains unclear. Dutrieux et al. describes a PML-mediated stabilization of the reverse transcription inhibitor hDaxx, while Kahle et al. detected no involvement of hDaxx in HIV-1 restriction (4, 5). Nevertheless, both studies indicate an

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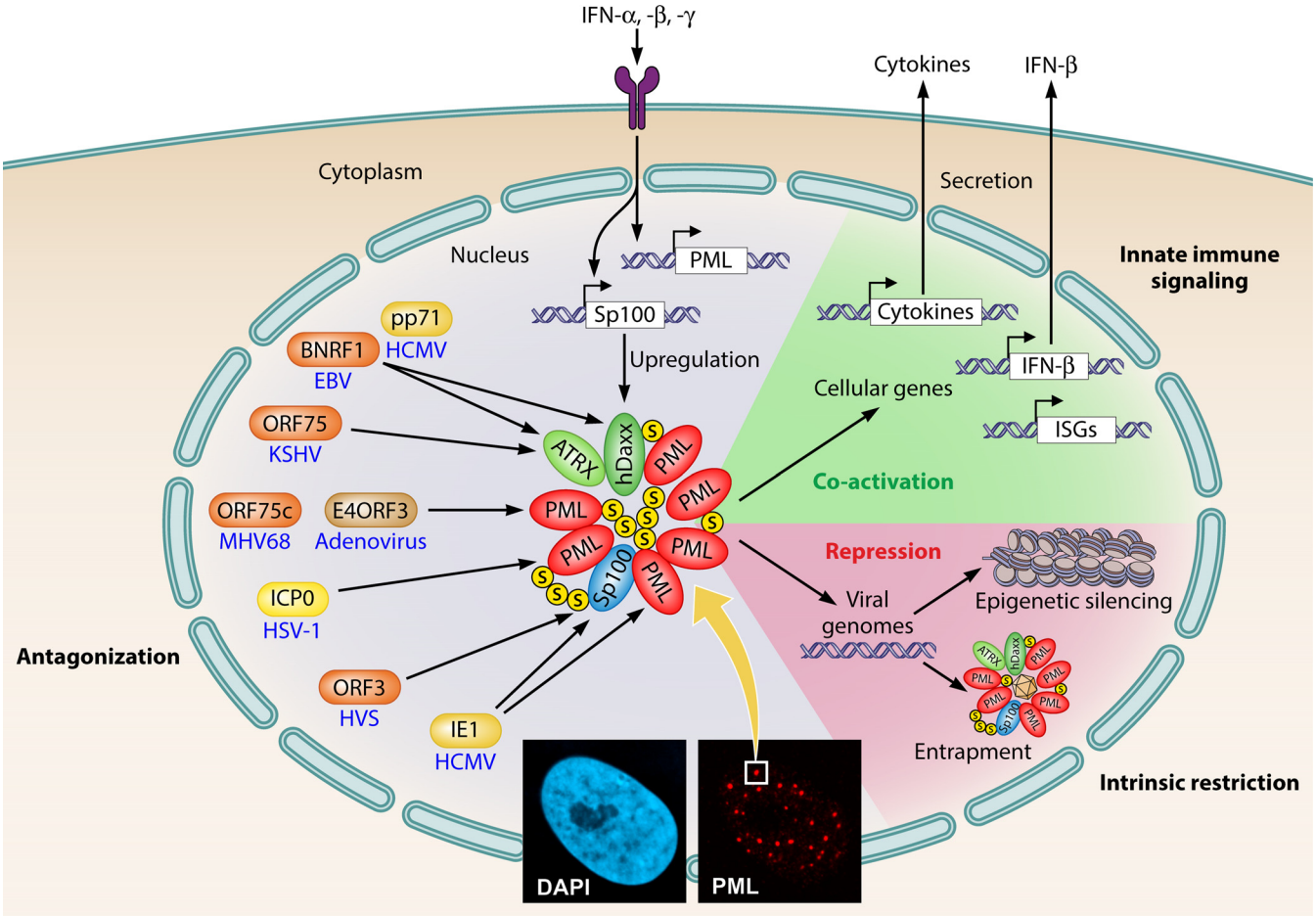

FIG 1 Role of PML-NBs in intrinsic and innate immune defense mechanisms and their antagonization by viral effector proteins. PML-NBs consist of multiple cellular proteins, including PML, Sp100, hDaxx, and ATRX, which can be modified by SUMO (denoted S in the figure) and accumulate in distinct foci within the cell nucleus (as illustrated by the immunofluorescence image of primary human fibroblast cells stained for PML). PML-NBs are able to mediate an intrinsic repression of viral replication by inducing epigenetic silencing of viral genomes or by entrapment mechanisms (lower right). In addition, PML-NBs are emerging as coactivators of cellular genes that exert antiviral activities, such as cytokines and ISGs, and PML-NB components are themselves upregulated by IFN treatment (upper right/upper middle). To overcome these antiviral activities, many viruses have evolved antagonistic proteins that affect individual PML-NB components or affect the whole cellular structure. Arrows indicate which PML-NB component is targeted by the respective viral factor (left). DAPI, 4′,6′-diamidino-2-phenylindole; EBV, Epstein-Barr virus; KSHV, Kaposi sarcoma-associated herpesvirus; MHV68, murine gammaherpesvirus 68; HCMV, human cytomegalovirus; HSV-1, herpes simplex virus type 1; HVS, herpesvirus saimiri; IFN, interferon; ISG, interferon-stimulated gene; S, SUMO, small ubiquitinlike modifier.

unconventional mobility of PML-NBs, which appear to sense viral nucleoprotein complexes or replication intermediates, resulting in movement of the respective proteins even to the cytoplasm. Additionally, PML and hDaxx were implicated as contributing to the control of retroviral latency via epigenetic repression (12, 13).

VIRAL PML-NB ANTAGONISTS

In order to overcome the restricting activities of different PML-NB components, viruses have evolved antagonistic effector proteins. Indeed, almost all viruses for which replication has been linked to PML-NBs encode regulatory proteins that employ different strategies to inactivate single NB components or disrupt the integrity of the whole structure (Fig. 1). Two well-studied examples are the ICP0 protein of HSV-1 and the immediate early protein IE1 of HCMV. ICP0 has been shown to act as a SUMO-targeted ubiquitin ligase (STUbL), inducing an immediate proteasomal degradation of SUMO-conjugated proteins, including NB components (14). This results in a rapid and very efficient antagonization of PML-NB-mediated silencing of viral gene expression. In contrast, IE1 uses a more gentle way to disarm PML-NBs. It specifically affects the SUMOylation of the restriction factors PML and Sp100 in a proteasome-independent manner (15). Since SUMOylation of PML is essential for the integrity of PML-NBs, this results in a dispersal and inactivation of PML-NB accumulations. The recent structural characterization of IE1 has revealed that the globular core domain of IE1 ($IE1_{CORE}$) shares secondary structure features of the conserved coiled-coil domain of tripartite motif (TRIM) proteins (16). Furthermore, our group has demonstrated that $IE1_{CORE}$ binds efficiently to the coiled-coil domain of PML, alternatively termed TRIM19. Consequently, via coiled-coil interactions, IE1 may not only inhibit the SUMOylation of PML but possibly affects other members of the TRIM E3 ligase family of innate immune regulators (16). In addition to IE1, HCMV encodes a second PML-NB antagonistic protein, the tegument protein pp71. This protein displaces the chromatin-associated factor, ATRX, from PML-NBs and degrades hDaxx in a

ubiquitin-independent but proteasome-dependent manner immediately after infection; however, the exact mechanism of this degradation is still unclear (6).

Another interesting example for the evolution of PML-NB antagonistic proteins can be found within the subfamily of gammaherpesviruses. All known gammaherpesviruses encode at least one conserved tegument protein that contains sequence homology to the cellular purine biosynthesis enzyme phosphoribosylformylglycineamide amidotransferase (FGARAT). While no enzymatic activities have been detected on these viral FGARAT homologous proteins (vFGARAT), various members of this family modify PML-NBs; however, they do so in different ways. For instance, the ORF75c protein encoded by murine gammaherpesvirus 68 (MHV-68) specifically induces the proteasomal degradation of PML (17). In contrast, ORF3 protein from herpesvirus saimiri degrades Sp100, BNRF1 from Epstein-Barr virus (EBV) disrupts the formation of the hDaxx-ATRX chromatin remodeling complex, and ORF75 from Kaposi sarcoma-associated herpesvirus (KSHV) degrades ATRX (18–20). In all examples studied, the respective modification of PML-NBs leads to a disabling of host cell intrinsic defenses; however, the PML-NB targets of vFGARAT proteins have diversified during evolution. On one hand, this indicates that the disarming of PML-NB-mediated intrinsic defense constitutes a critical event in the replication of all herpesviruses. On the other hand, the selective antagonization of individual PML-NB components by gammaherpesviruses may reflect that these viruses utilize specific functions of the cellular PML-NB repression machinery to promote latency as the default outcome of infection. So far, this appears to be unique to the gammaherpesviruses, since our recent studies on the role of PML-NBs during human cytomegalovirus latency do not reveal a major contribution of PML, Sp100, or hDaxx to the establishment of latent infections (21).

Adenoviruses also encode potent PML antagonistic proteins. In particular, structural characterization of the E4-ORF3 protein has revealed that this protein has the propensity to assemble in linear and branched oligomeric chains that form a multivalent, cablelike matrix within the nuclear volume. This assembly creates avidity-driven interactions with PML and other tumor suppressor proteins which disrupt PML-NBs and inactivate the function of the respective proteins (22). However, not all viruses that are restricted by PML-NBs have been shown unequivocally to encode antagonistic viral proteins. For instance, infection with the polyomavirus BK virus (BKV) has been shown to disperse Sp100 and hDaxx from PML-NBs (23). Furthermore, BKV is able to rescue the growth of an ICP0-null herpes simplex virus 1 mutant, strongly suggesting that BKV encodes a factor that substitutes for the PML-NB disrupting function of ICP0. However, the respective function has not yet been ascribed to a defined BKV protein.

In conclusion, PML-NBs act by various mechanisms to inhibit distinct stages of viral replication, relying on the activities of different NB constituents and their isoforms. In turn, viruses have evolved complex strategies to inactivate repressive NB proteins, while at the same time they may recruit and take advantage of specific NB components.

PML AND INNATE IMMUNE SIGNALING

An emerging theme in virology research is the role of PML in the regulation of innate immune signaling. The interplay between PML-NBs and innate immunity was first discovered with the observation that interferon (IFN) treatment induces an upregulation of several NB proteins, including PML and Sp100, and enhances their antiviral activity. In addition, PML depletion reduces the capacity of IFNs to protect from viral infections, indicating an important contribution of PML-NBs to the establishment of an IFN-induced antiviral state (24, 25). Further results by our and other groups suggest an even closer cross talk, since they implicate PML as a direct, positive regulator of IFN signaling (26–28). Type I (alpha interferon [IFN-α] and IFN-β) and type II (IFN-γ) IFNs induce the expression of interferon-stimulated genes (ISGs) through intracellular signaling cascades that eventually lead to the association of activated signal transducer and activator of transcription (STAT) complexes with ISG promoter regions. Evidence exists that PML has the capacity to modulate different stages of this signaling pathway, since it can enhance the expression of IFN-β and, additionally, is required for efficient IFN-induced transcription of ISGs (Fig. 1) (29). This holds true for numerous ISGs regulated by type I IFNs, as well as for IFN-γ-induced major histocompatibility complex (MHC) class II genes (26–29), while controversial results are available concerning MHC class I gene expression (30, 31). Interestingly, IFN-γ treatment induces an increased spatial proximity between PML-NBs and the MHC class II gene cluster. This topology is maintained long after IFN stimulation and correlates with a sustained transcription-permissive epigenetic state of the MHC class II gene *DRA* (32). Thus, PML-NBs may generate a transcriptional memory that facilitates rapid gene expression upon IFN-γ restimulation.

The molecular mechanisms by which PML stimulates the IFN pathway are far from being fully understood, but they appear to depend on the modulation of downstream signaling events taking place in the cell nucleus. In particular, PML has been found to associate with transcription factor complexes that control IFN and ISG expression, resulting in stabilization of their components and in enhanced promoter occupancy (26, 27, 29). Intriguingly, these activities correlate with specific interactions of the individual PML isoforms, which can be attributed to their unique C-terminal domains. The PML isoform II (PML II) seems to be of particular importance, as it undergoes interactions with different components of type I and type II IFN signaling pathways. PML II but no other PML isoform binds and recruits the MHC class II transactivator CIITA to PML-NBs, thus leading to stabilization and prolonged activation of the transactivator (26). Furthermore, PML II directly associates with transcription factors like interferon regulatory factor 3 (IRF3) and STAT1 and promotes their recruitment to IFN-β and ISG promoters, respectively (29). PML isoform IV has also been reported to enhance the activity of IRF3, thereby participating in IFN-β production during VSV infection (33). However, this is achieved through a different strategy that involves recruitment of the peptidyl-prolyl isomerase Pin1 to PML-NBs and prevention of Pin1-mediated IRF3 degradation, thus highlighting the complex role of PML in the regulation of IFN signaling.

Finally, there is evidence that the coregulatory function of PML in innate immune signaling not only affects IFNs but targets an extended spectrum of cytokines. For instance, the production of the proinflammatory cytokines interleukin 1β (IL-1β) and IL-6 has been reported to be markedly decreased in PML-deficient cells (34, 35). In accordance with a deregulation of IL-6 that has a prominent role in the acute-phase response, PML knockout mice display an aberrant immune response to bacterial infections and

are resistant to acute lipopolysaccharide (LPS)-mediated lethality (34). These data encourage the hypothesis that the coregulatory role of PML in innate immune signaling may be even broader than anticipated from previous studies and may include thus-far-unrecognized biological functions, such as the regulation of acute inflammatory responses during viral infections.

CONCLUSION

Consistent with the recently recognized importance of many TRIM family members for innate immune signaling, PML emerges as a significant coregulator of the IFN pathway. This further accentuates an as-yet-enigmatic functional dichotomy of PML-NBs during viral infection. On one hand, PML-NBs act as powerful repressors that induce a silencing of viral gene expression. On the other hand, these structures serve as coactivators of cellular genes that have antiviral activity (Fig. 1). Further studies will be necessary to mechanistically understand how PML-NBs mediate these complementary effects via at-first-glance contradictory mechanisms. However, as a consequence, viral antagonists of PML-NBs may have evolved not only to overcome the intrinsic restriction of PML-NBs but also to specifically inactivate an IFN-stimulating function of PML. This has already been demonstrated for the HCMV IE1 protein, which blocks IFN signaling during HCMV infection via binding PML (27, 28). In conclusion, targeting PML-NBs likely represents a common viral strategy to antagonize both intrinsic and innate immune mechanisms.

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